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Editorial
Brain Tumors and Artificial Sweeteners? A Lesson on Not Getting Soured on Epidemiology

A controversial report has been published recently concerning brain tumor incidence rates in the United States and a potential link with aspartame [1], an artificial sweetener used in several foodstuffs since the early 1980s. Using 1975 to 1992 incidence data from the Surveillance, Epidemiology, and End Results (SEER) program, Olney et al. [1] examined temporal trends for all central nervous system tumors (CNS) combined, as well as specific brain tumors including astrocytomas, glioblastomas, and medulloblastomas. For all CNS tumors combined, there was a marginal increase from 1975 to 1977 (45–49 tumors/million), a plateau from 1977 to 1984 (48/million), a slight increase from 1984 to 1985 (47–53/million), and then another plateau from 1985 to 1992 (53/million). When specific tumor sites were examined, the authors noted that the incidence of astrocytomas increased by 50% from 1975 to 1977, plateaued until the mid-1980s, and then precipitously dropped. In contrast, the incidence rates of glioblastoma were almost the exact reciprocal of the astrocytomas (i.e., decreasing, stable, and then notably increasing over time). Since astrocytomas can progress to glioblastomas, the authors argue that the availability of computerized tomography scans (i.e., earlier detection) likely accounted for the upward shift in astrocytomas and the downward shift in glioblastomas around 1977. However, during the 1980s, there was an upward shift in glioblastomas and a downward shift in astrocytomas, even though improved detection methods (e.g., magnetic resonance imaging) were continuing to become available. With additional examination of survival data, the authors argue that this shift likely represents a real increase in the rate of conversion of astrocytomas to glioblastomas. From these data they build an argument that the increase in brain tumor incidence may be due to the appearance of aspartame in the early 1980s. Included in their discussion are three elements the authors use to invoke a potentially causal relationship: (a) animal data that suggest a potential link between aspartame and brain tumors (data on file at the Food and Drug Administration's Hearing Clerk's office); (b) the description of an in vitro study which suggests that aspartame may be nitrosated upon ingestion, which then could result in a nitrosurea-like molecule [2] (since nitrosureas have been established as causative agents of brain tumors in animals [3–5]); and (c) the authors' analysis of the SEER program data. They conclude that a reassessment of the potential carcinogenicity of aspartame is an urgent matter.

From an epidemiologic perspective, the conclusion of this report may well represent a classic example of an ''ecologic fallacy'' [6], because the Olney et al. study was a correlative analysis (i.e., ecologic analysis) that demonstrated that two events occurred during roughly the same time period. There is no information available regarding whether the individuals who developed brain tumors consumed aspartame. For example, one might also invoke (a) cellular phone, home computer, and VCR usage; (b) depletion of the ozone layer; or (c) increased use of stereo headphones as potentially causative agents to argue trends in brain tumors and the changing environment. All such events could potentially be positively correlated with brain tumor incidence, and some or all of these possibilities may or may not have any biological plausibility to the observed associations. It is quite possible that the increase in brain tumors over the past few decades might not all be explained by increased surveillance and detection, and aspartame cannot be ruled out as a causal factor. However, it is impossible to draw an appropriate conclusion when correlative data are used; these types of studies can only be viewed as hypothesis generating.

This study has raised a broader issue: how does one determine causality from an epidemiologic study? Study design is extremely important. In order to test a hypothesis, individual data must be collected and epidemiologists typically use a case-control or cohort approach. Although there are some differences of opinion regarding determination of whether exposure x causes disease y, individuals generally agree that certain criteria should be satisfied. Some of the widely used criteria for determining causality include (a) a temporal relationship (Does the exposure definitely come before the disease?), (b) a dose-response relationship (Is more exposure associated with more disease?), (c) strength of association (Is the ratio of the disease in those exposed compared to those unexposed of a high magnitude?), (d) consistency (Do researchers at other institutions, in other populations and in other countries, report similar results?); and (e) biological plausibility (Does it make biologic sense?) [reviewed in reference 7].

In the study conducted by Olney et al. [1], there was almost a simultaneous relationship observed between the introduction of aspartame and a rise in brain tumor incidence rates; thus the temporal relationship is very weak. Lack of individual data precludes evaluation of dose-response relationships and strength of association. Since

there have yet to be any analytic studies (case-control, cohort) that demonstrate an increased risk of brain tumors with aspartame exposure, no consistency has been established. Finally, the biologic evidence evaluating the carcinogenicity of aspartame is equivocal; the FDA commissioner concluded in the mid-1980s that aspartame was not associated with brain tumor development in rats [8].

Even when reporting on well-designed and well-analyzed studies, most epidemiologists tend to be highly conservative in claims that their data speak the truth. Discussion sections in epidemiologic publications usually contain the added qualifiers and cautions warranted in data interpretation; similar caution would be advised in considering the Olney et al. report.

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Dr. Olney Comments:

My colleagues and I agree with Dr. Ross's analysis of our study. It is a work that provides new information about increases in the incidence and malignancy of brain tumors in a large human population. In addition, it sets forth a hypothesis regarding a possible cause and calls for research to test the hypothesis. Dr. Ross appropriately cautions that ecological correlation is a very weak argument for a causal association. However, it is important to recognize that while our recent study was primarily an ecological study, our hypothesis rests on laboratory results 15 years ago that predicted an increase in brain tumors. Because of space limitations, I was not able to elaborate this evidence adequately in our recent article.

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